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FORMULATION AND EVALUATION OF SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM FOR ANTIHYPERLIPIDEMIC DRUG

Anuja G. Gawai*, Sandip C. Atram, Rupali P. Sable, Vrunda J. Rajput, Subhod A. Urkunde.
Department of pharmaceutics, Vidyabharati College of Pharmacy, Amravati – 444 602, India

*Corresponding Author's E mail: anujagawai98@gmail.com
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ABSTRACT

The aim of this study is to develop an anti-hyperlipidemic, orally soluble atorvastatin. This is a BCS Class II drug. Development of atorvastatin providing improved bioavailability and reduced variability is required. It was prepared by ultrasonic method. The content of the selected drug (SBF4) is 98%, which represent the highest concentration of the drug currently in production. The presence of surfactants and co-surfactants provides greater stability with increased drug release. Development of self-nanoemulsifying drug delivery system (SNEDDS) formulations to improve the solubility and release rate of poorly soluble hypolipidemic drugs. Among the formulations, BF2, BF4 and BF6 showed the highest concentration of 85.10 ± 1.23%, while the commercial formulation showed only 58.49 ± 1.22 cumulative drug release after 90 min. This is the larger drug spread for SNEDDS selection. The aim of the current study is to prepare a stable dose of atorvastatin calcium that improves drug partitioning compared to the existing commercial product (Lipitor 10 mg) and finally differs in oral bioavailability and absorption and reduction in patients. Effects of nutrients on absorption Comparison of drugs with commercial products.

Keywords: BCS, SNEDDS, BF2, BF4, BF6, SBF4

INTRODUCTION

Nanoemulsions are sometimes referred to as "near thermodynamically stable" because the droplets are highly susceptible to emulsification or dissolution, agglomeration, and coalescence due to Brownian motion, reduced gravity, and droplet deformation. Emulsification of the drug in the intestine facilitates its oral administration, making it an ideal drug delivery system.[1]

This is a new way to improve the oral bioavailability of poorly soluble drugs. Self-nanoemulsifying drug delivery system (SNEDDS) is a technology used to improve the solubility and bioavailability

of poorly soluble drugs. Use of SNEDDS for antilipidemic drugs may increase the absorption of these drugs.[2]

Antihyperlipidemic drugs are drugs that help lower lipids (fats) in the blood, especially cholesterol and triglycerides. This medication is used to treat hyperlipidemia, a condition in which high lipids are present in the blood and is a major risk factor for cardiovascular diseases such as heart attack and stroke. SNEDDS documents nanoemulsions due to the diffusion of hydrophilic cosolvents or cosurfactants from the organic phase to the aqueous phase, creating turbulence and forming nanosized droplets with ultra-low interfacial tension [3-5]. SNEDDS are the most popular and reliable delivery vehicles for hydrophobic drugs with low bioavailability. SNEDDS has also been used to deliver bioactive ingredients.[6] Antihyperlipidemic drugs are drugs that help lower lipids (fats) in the blood, especially cholesterol and triglycerides. There are several classes of antihyperlipidemic drugs, each with their own mechanism of action and effects on lipid metabolism [7-10]. Self-nanoemulsifying drug delivery system (SNEDDS) is a technology used to improve the solubility and bioavailability of poorly soluble drugs. Regarding lipid-lowering drugs, the use of SNEDDS may increase the absorption of these drugs.[11]

Although liquid SNEDDS has many advantages, there are also issues such as chemical/product precipitation during storage and interaction between fillers and the capsule shell. This is not good. This is one of the problems they face such as formulation stability during pre-storage. The main strategy to solve these problems is to change the SNEDDS fluid to solid SNEDDS standards. In general, techniques used .[12]

MATERIALS AND METHODOLOGY

MATERIALS:

Atorvastatin was gifted by Dr Reddy Laboratory Mumbai, PEG 400 & PEG 600 was supplied by Loba Chem Mumbai, Sunflower oil purchased from Namita Organic Food Mumbai, other chemicals such Tween 80 & Tween 20, 0.1 N Hcl were supplied by SDFCL estate worli Mumbai.

METHODS

Investigation of Atorvastatin Solubility in Different Ingredients

The solubility of atorvastatin in different oils, surfactants, co-surfactants or mixtures of oils and surfactants is determined according to this method. Add excess solution, 2 g to each client's choice (or combination), into a glass vial with a glass cap. Vortex the sample to thoroughly mix the solution

and carrier. The vial was shaken for 48 hours in an isothermal shaking water bath set at 25°C. Equal sample was then centrifuged at 5000 rpm for 15 min to remove unsolvated substances. Aspirate the supernatant and filter through a 0.45µm filter. A portion of the supernatant was appropriately diluted with methanol, and the concentration of atorvastatin was determined spectrophotometrically at 246 nm against a blank prepared from each excipient in methanol. The test was repeated three times.[13]

Construction of Psedo ternary phase Diagram

A ternary phase diagram was constructed to identify the region where the sample could self-emulsify under dilution and gentle mixing. Additionally, it would be useful to create a ternary diagram to determine the relative composition of the different SMEDDS oil phases, surfactant, and co-surfactant [14]. Sunflower oil was selected as the oil phase based on the solubility study of atorvastatin. Tween80, Tween20 and Tween80 are used as surfactants, while PEG 400 is used as the second surfactant. Use distilled water as the aqueous phase to draw these phase diagrams. Different types of oil phase, surfactant and co-surfactant were prepared and divided into three groups. Surfactant and co-surfactant (Smix) in each group were mixed in different weights (1:1, 2:1, 3:1) [15].

Method of Preparation for Antihyperlipidemic drug loaded SNEDDS

To prepare drug-loaded SNEDDS according to the phase diagram, the SNEDDS formulation containing an appropriate amount of oil phase and a small amount of surfactant, which needs to be completely diluted with water, is selected. Drug-loaded SNEDDS is called SNEDDS preconcentrate. Measure the amount of atorvastatin equal to the dose, dissolve it in the oil phase (sunflower oil) in a constant temperature water bath at 45°C, and add the amount of surfactant (Tween 80) and co-surfactant (PEG 400). The mixture is then sonicated until a clear mixture is obtained. Samples were equilibrated at room temperature for at least 48 hours until further use. Follow the same procedure to prepare SNEDDS preconcentrates for all selected oils and Smix combinations. The composition of the drug-loaded SNEDDS formulation is shown in Table 1.[16]

Table 1 Formulation of Drug loaded SNEDDS

Sr	Formulation code	Drug (mg)	Oil (%)	Surfactant (%)	Cosurfactant (%)
1	BF1	10	5	47	47
2	BF2	10	5	63	31.5
3	BF3	10	10	45	45
4	BF4	10	10	60	30

5	BF5	10	15	42	42
6	BF6	10	15	56.6	28
7	BF7	10	20	40	40
8	BF8	10	20	53.33	26.66

Conversion of Liquid- SNEDDS to Solid SNEDDS

Preparation of solid SNEDDS[17]

The liquid has been made into a product to improve the quality of SNEDDS and the batch numbers are SBF1, SBF2, SBF4, SBF6, these are the quality products of SNEDD liquid. Atorvastatin product SNEDDS is prepared by mixing liquid SNEDD samples with different adsorbents. Mix liquid formulation fixed adsorbent Avicel PH 101 with liquid SNEDDS in a weight ratio of 1:0.25, 1:0.5, 1:1 and 1:1.5.

Table 2: Composition of optimised liquid Atorvastatin SNEDDS formulation

Sr	Formulation code	Drug (mg)	Oil(%)	Surfactant (%)	Cosurfactant (%)
1	SBF1	10	5	47	47
2	SBF2	10	5	63	31.5
3	SBF4	10	10	60	30
4	SBF6	10	15	56.6	28

Due to the good adsorption properties of Avicel, liquid SNEDD can be converted into solid SNEDD. Add SNEDD dropwise to a large bowl containing Avicel PH 101. After adding, homogenize the mixture using a glass rod to ensure even distribution.

Characterization of Antihyperlipidemic drug loaded SNEDDS

Average Droplet Size [18]

The average droplet size (ADS), polydispersity index (PDI) of the prepared SNEDDS preconcentrates were determined with a Zeta sizer (Malvern Instruments) according to the dynamic light scattering (DLS) law. SNEDDS preconcentrate was diluted 50-fold (1:50) using distilled water and measured on a Zeta particle sizer.

Zeta potential polydispercity[19]

The zeta potential of the SNEDDS preconcentrate preparation was determined by a Zeta sizer (Malvern Instruments) working on the principle of dynamic light scattering (DLS).

Thermodynamic stability test[19]

For thermal stability testing, each SNEDDS preconcentrate was diluted up to 50 times with distilled water and the prepared nanoemulsion system was subjected to the following tests.

A) Centrifugation test For centrifugation, collect all preparations in separate centrifuge tubes and centrifuge at 3500 rpm for 20 minutes. All formulations were then observed for phase separation and emulsification.

B)Heating cooling cycle (H/C cycle) test

The formulation is exposed to heat and cold. All formulations were stored between 40°C and 45°C for 24 hours. The formulation is then found for any instability (phase separation, blurriness, etc.).

Percentage transmittance determination [20]

Measure the percent transmittance on a UV spectrophotometer to determine transparency. All SNEDDS preconcentrates were diluted 50-fold with distilled water. The percentage at 246 nm was measured in a UV spectrophotometer using distilled water as the blank. The results of the decision spread percentage are reported in the Result and Discussion section.

Cloud point determination [21]

The cloud point is the temperature at which the nanoemulsion system becomes unstable and cloudy due to dehydration of the nonionic surfactant. This is exactly the phase reversal point of the nanoemulsion system. Air temperature measurement of stability of nanoemulsion systems. SNEDDS concentrate is diluted 10-fold with distilled water in a glass bottle. The resulting nanoemulsion is then heated and the turbidity is visually observed by gradually increasing the temperature. The temperature at which the first sign of cloudiness appears is recorded as the cloud point temperature of the preparation. This process was done three times to confirm the accuracy of the cloud point.

Test for robustness to dilution[21]

The prepared SNEDDS concentrate should be potent when diluted in different pH environments. To evaluate this situation, 1 ml of SNEDDS preconcentrate is diluted 100 times (1:100) with 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8) and precipitation, phase separation, turbidity and percentage spread are observed for 24 hours is provided.

Self-emulsification test [22]

All prepared SNEDDS preconcentrates were tested to determine the ease of nanoemulsification. Take 250 ml of pure water in a beaker and stir continuously at 50 rpm. The temperature is controlled at 37 ± 0.5 °C. Then, 1 ml of SNEDDS preconcentrate was added here and the time required for clarity and emulsification was observed. The resulting emulsion was graded as follows:

Table 3: Grade of Emulsion

Sr	Grade	Resultant appearance of emulsion
1	Grade A	Rapid forming transparent system, (very easily nanoemulsified)
2	Grade B	Rapid forming translucent system, (efficiently nanoemulsified)
3	Grade C	Turbid or milky system, (poorly nanoemulsified)
4	Grade D	Milky & phase separated system, (not able to emulsify)

Drug content determination [23]

To determine the total drug content in SNEDDS, 1 ml of SNEDDS preconcentrate was taken and dissolved in 25 ml of methanol to extract the loaded drug (atorvastatin). This solution is then diluted appropriately and analyzed in a UV spectrophotometer at 246 nm using a standard calibration curve of atorvastatin in methanol using methanol as a blank control.

FTIR Studies

Atorvastatin samples were analyzed at cm-1 in an FTIR spectrophotometer. FTIR spectra were recorded and compared with the reference spectrum of the drug.

In-vitro drug diffusion study of SNEDDS [24]

In-vitro drug diffusion study in 0.1N HCl

In vitro diffusion studies were performed on selected SNEDDS samples using a dialysis technique in comparison with a commercially available sample (Lipitor 10 mg). First, the dialysis membrane (dialysis membrane-150; LA401-5MT; average diameter 25.4 mm, average width 42.44 mm, purchased from HiMedia Laboratories, Mumbai, India) was washed with running water for 2 hr. It was then placed in release medium (0.1 N HCl) for 24 hours. One end of the water filter is tied with a thread. Finally load 1 ml of SNEDDS preconcentrate into the filter and dilute to 15 ml with 0.1 N HCl. Then do the same tide check at the other end to make sure there are no leaks. The filter bag was placed in 250 ml of 0.1 N HCl at a speed of 200 rpm and a temperature of 37± 0.5 °C. Take 5ml samples at scheduled times (5 minutes, 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 60 minutes, 70 minutes, 90 minutes).After removal of each sample, an equal volume of fresh 0.1 N HCl was added to control the water bath. The sample was filtered and appropriately diluted with 0.1 N HCl, and the chemical content was analyzed with a UV spectrophotometer at 246 nm according to the standard calibration curve of atorvastatin in 0.1 N HCl. Similarly, for commercial production, the equivalent of tablet powder is dissolved in 15 ml of 0.1 N HCl, filtered and dialyzed. Fill the dialysis membrane and analyze the in vitro diffusion profile of the drug as described above.

different adsorbents. The liquid formulations fixed adsorbent Avicel PH 101, to liquid SNEDD's ratios by weight 1: 0.25 , 1:0.5 , 1:1 , 1: 1.5 mixing was performed .

Characterization of Solid SNEDDS

Drug Content :

To determine the total content of drug in the SNEDDS product, take 10 mg of the SNEDDS product (equivalent to 10 mg of atorvastatin) and dissolve in 25 ml of methanol plus drug (atorvastatin). This solution is then diluted appropriately and analyzed in a UV spectrophotometer at 246 nm using a standard calibration curve of atorvastatin in methanol using methanol as a blank control. Drug content determination results are reported in the results table and discussion section.

In vitro dissolution [24]

Different drug-loaded atorvastatin SNEDDS products prepared with different carriers were dissolved in phosphate buffer at pH 6.8, and their degradation rates were compared with pure drug. The dissolution profile showed that 90 seconds after the onset of dissolution, the hard gelatin capsule disintegrated and released its contents. Different SNEDDS products showed the highest percentage of drug release within 90 min, but the isolation study was continued for 1 h to identify any precipitates or

changes that may occur over time. In the standard pharmacopoeia for the separation of active substances in capsules, at least 80% of the active ingredients must enter the drug within 90 minutes.

Stability study [25]

If the formulation is not stable during long-term storage, it may cause the drug to become unstable. Breakdown or degradation of the drug during storage may reduce the drug concentration in nanoemulsion systems. The physical properties of nanoemulsions may also change due to structural instability. Therefore, to evaluate the stability, the ideal nanoemulsion formulation was filled into glass vials and stored at room temperature (25 ± 20°C) for 2 months. After two months, the formulations were evaluated for chemical content, physical appearance (e.g. transparency and phase separation), particle size, polydispersity index (PDI), and light transmittance.

RESULT AND DISCUSSION

Solubility of drug in oil, surfactant and co-surfactant

To develop stable nanoemulsion systems, oils, surfactants and co-surfactants must have high solubility ability for drugs. Determination of the solubility of atorvastatin in different oils, surfactants and co-surfactants. Sunflower oil is included in the system due to its good solubility properties. After the water medium enters the self-microemulsification system, a good oil-water emulsion can be formed with only gentle stirring. Surfactants and cosurfactants preferentially adsorb at the interface, reducing interfacial energy and providing a mechanical barrier to coalescence.

Table 4 : Solubility of ATV in oil

Sr no	Vehicle	Solubility (mg/ml)
1	Olive oil	08.25
2	Sunflower oil	29.25
3	Soyabean oil	25.25
4	Palm oil	20.25
5	Capmul	10.25
6	Groundnut oil	05.25

Screening of of Surfactant & cosurfactant

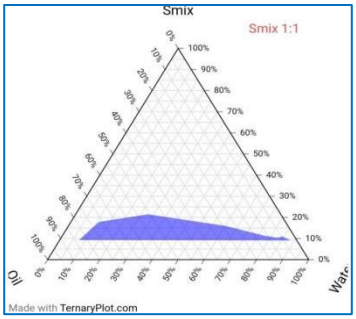
To develop stable nanoemulsion systems, oils, surfactants and co-surfactants must have high solubility ability for drugs. Determination of the solubility of atorvastatin in different surfactants and co-surfactants. Solubility data for atorvastatin are listed in Table 5.

Table 5 : Solubility of Surfactant and Cosurfactant

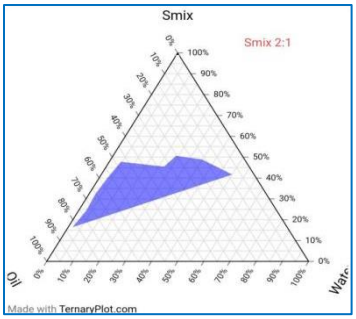
Sr	Surfactant	Solubility in (mg/ml)
1	Tween 80	68.999±1.56
2	Tween 20	34.59±2.34
	Cosurfactant	
1	PEG 400	93.39±1.52
2	Polyethylene glycol	48.99±1.54

Phase Diagram

A pseudo-ternary phase diagram was created to determine the maximum microemulsion area in the diagram and the mixture of excipients (oil phase and Smix ratio) that gave the maximum dilution line. The largest microemulsion area can be easily found in the formula composition. A line with a fully dilutable oil/Smix mixing ratio will ensure the stability of the microemulsions formed when diluted with gastrointestinal (GI) fluids. Highly dilutable batch. A ternary phase diagram was developed to define the self-emulsifying region and determine the optimal combination of oil, surfactant, and cosurfactant. It can be seen from the phase diagram that the self-emulsifying area increases when the surfactant concentration increases. As the co-surfactant concentration increases, the emulsified area decreases. When the surfactant concentration is more than 50%, the self-emulsifying effect is good. By design, phase separation occurs in the SNEDDS formulation as the oil concentration increases (more than 35%). BF8 shows that the increase in viscosity shows that the viscosity of the system increases as the oil and surfactant concentration increases, forming a clear emulsion with increasing co-surfactant (PEG 400) concentration. A ternary phase diagram was developed to define the self-emulsifying region and determine the optimal combination of oil, surfactant, and cosurfactant. It can be seen from the phase diagram that the self-emulsifying area increases when the surfactant concentration increases.



Smix 1:1



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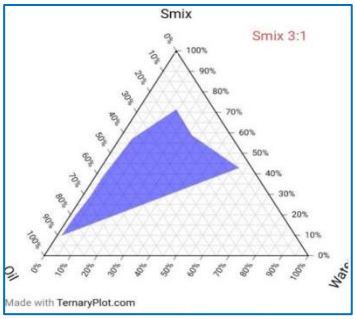

Smix 3: 1

Characterization

Average Droplet size and Zeta potential

Among the formulations, the average pellet size of atorvastatin-loaded SNEDDS was 90.37, and the formulation with a PDI value of 0.263 showed a lower PDI than the value, showing a homogeneous size distribution mv . SNEDDS formula contains non-ionic ingredients and negatively charged sunflower oil.

Table 6 : Droplet size , PDI , SNEDDS Formulation

Formulation Code	Droplet Size	Poly Dispersity Index	Zeta Potential(mv)
BF1	85.82	0.166	-18.5
BF2	90.37	0.263	-19.5
BF4	160.2	0.175	-23.4
BF6	189.2	0.297	-27.5

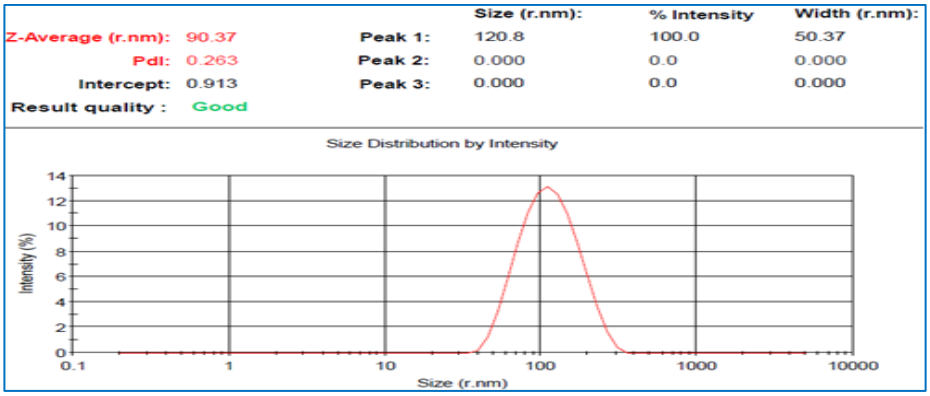

Fig. 1: Particle Size Distribution

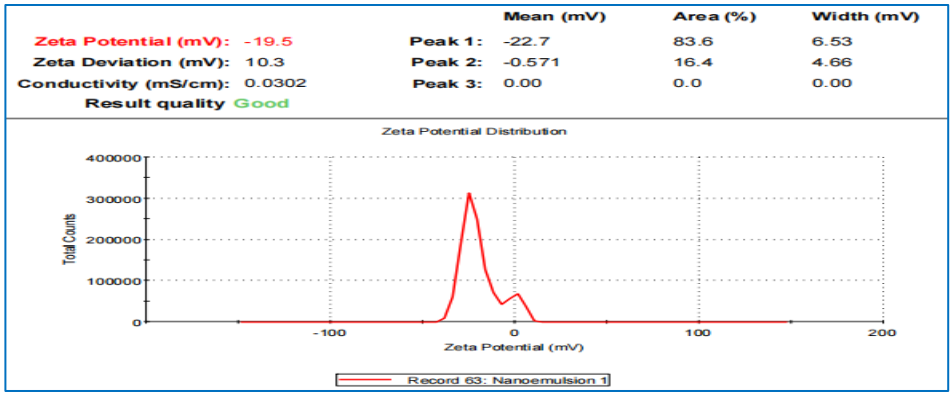

Fig. 2: Zeta potential

Thermodynamic Stability :

Centrifugation test: Thermodynamic stability studies aim to identify and avoid metastable compounds. The formulation remained stable during centrifugation at 3500 rpm with alternating temperature cycles of 40°C and -4°C. No phase separation or precipitation was observed.

Table 7: Stability test

Formulation code	Centrifugation test	Heating Cooling cycle test	Percentage Transmittance
BF1	No phase Separation or creaming	Stable	92.3%
BF2	No phase Separation or creaming	Stable	94.3%
BF3	No phase Separation or creaming	Stable	93.8%
BF4	No phase Separation or creaming	Stable	92.1 %
BF5	No phase Separation or creaming	Stable	93.9 %
BF6	No phase Separation or creaming	Stable	98.9 %
BF7	Phase Separation or creaming	Unstable	90%

Cloud point measurement:

All formulations have a very high turbidity around 80°C. In all formulations, cloudiness reverses after a few minutes. Phase separation and precipitation may occur due to dehydration of the POE moiety and the alkyl chain of the surfactant system.

Table 8. Cloud point of stable SNEDDS formulation

Formulation code	Cloud point
BF1	73±6.52
BF2	74±5.15
BF3	77±5.8
BF4	80±4.64
BF6	76±4.64

Self Emulsification Time:

In this study, the formulations (BF1-BF8) show spontaneous emulsification and good stability without any signs of drug or excipient precipitation.

Table 9. Selfemulsification time of various SNEDDS formulations

Formulation code	0.1N Hcl		Distilled Water	
	Emulsification time (sec)	Grade for Emulsification	Emulsification time (sec)	Grade for Emulsification
BF1	64	Grade B	74	Grade B
BF2	57	Grade A	62	Grade B
BF3	78	Grade B	93	Grade B
BF4	71	Grade B	85	Grade B
BF5	86	Grade B	98	Grade B
BF6	77	Grade B	110	Grade C
BF7	101	Grade C	120	Grade C
BF8	82	Grade C	115	Grade C

Drug content:

Calculate the chemical content of the selected sample using the standard formula. The percentage of drug content of the preparation is indicated in the table. BF4 & BF6 products in the table have the highest chemical content. Here, the ratio of oil to surfactant in the drug in the formulation was found to be in the range of 90 to 99, which shows a uniform distribution.

Table 10 : Percentage of drug in various formulations

Formulation Code	Percentage of Drug
BF1	97.29
BF2	97.4
BF3	97.7
BF4	98.5
BF5	97.9
BF6	98.9
BF7	98.67
BF8	98.29

Physical Analysis of globules:

Transmission electron micrographs show clear formation of spherical surfaces with well-defined boundaries in the presence of water, similar to that observed in the new atorvastatin-loaded SNEDDS. Droplet sizes were found to range from 8 nm to 200 nm, confirming the results obtained by zeta size measurment.

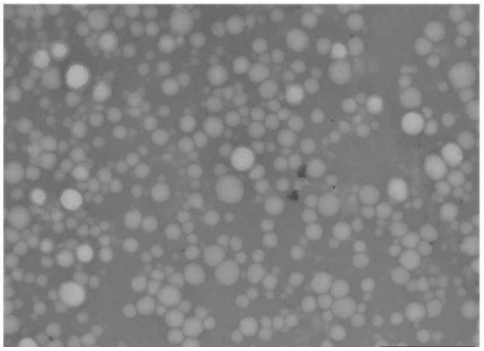

Figure 3 : TEM Image of droplet

FTIR studies :

Possible effects of hydrogen bonding between atorvastatin molecules were observed from the spectra. The spectrum of pure atorvastatin is comparable to that obtained with SNEDDS, indicating that supplied gift sample is of atorvastatin and there is no interaction they were compatible with selected ingredient.

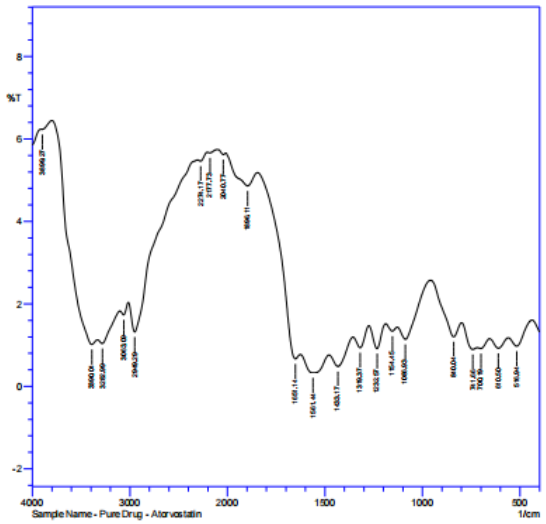

Fig 4 : Specta of pure drug atorvastatin

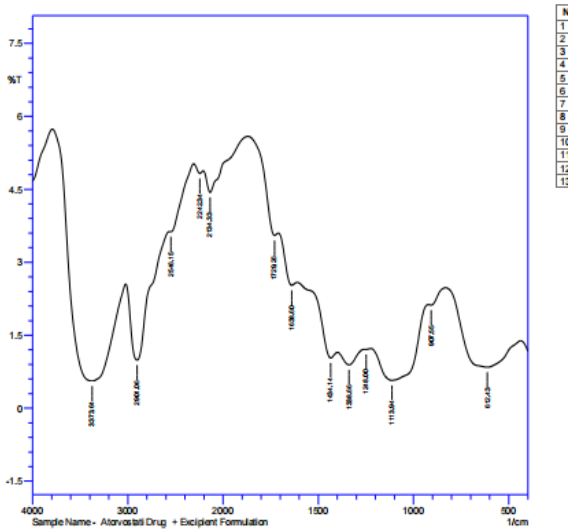

Fig 5 : Spectra of Formulation of nanoemulsion

In vitro drug release Test

The percentage of atorvastatin release in BF4 and BF6 formulations was found to be higher than other formulations and commercial products (Lipitor 10 mg). The drug release percentage of BF4 and BF6 after 90 minutes was 91.49% and 88.63%, respectively, while the release rate of the commercial product was 58.49%. The drug release percentage is higher in the BF4 formulation due to lower viscosity and higher surfactant concentration.

Table 11: In vitro drug release of SNEDDS

Time (Min)	**Cumulative percentage drug release (%) in 0.1N HCl**				
	BF1 (Mean±SD), n=3	**BF2** (Mean±SD), n=3	**BF4** (Mean±SD), n=3	**BF6** (Mean±SD),	**Marketed formulation** (Mean±SD)
0	0	0	0	0	0
5	24.86±0.49	26.61±0.87	30.76±1.01	32.47±1.02	2.86±0.35
10	36.32±0.85	32.71±1.21	35.98±0.95	48.71±1.21	22.64±0.59
20	41.24±0.73	45.11±0.78	50.09±0.75	66.71±1.21	26.64±0.92
30	49.25±0.98	51.20±1.41	64.69±1.16	73.06±0.95	28.63±0.88
40	54.21±0.98	56.71±1.21	76.34±1.02	78.06±0.95	40.86±0.85

50	57.67±1.06	65.06±0.95	79.68±0.88	80.97±0.92	46.42±1.09
60	58.19±0.92	69.35±1.13	87.97±0.92	83.97±0.92	48.34±1.15
75	62.78±1.43	78.46±1.55	90.76±1.28	87.63±0.88	56.34±1.15
90	67.06±1.12	85.10±1.23	91.49±1.43	88.63±0.88	58.49±1.22

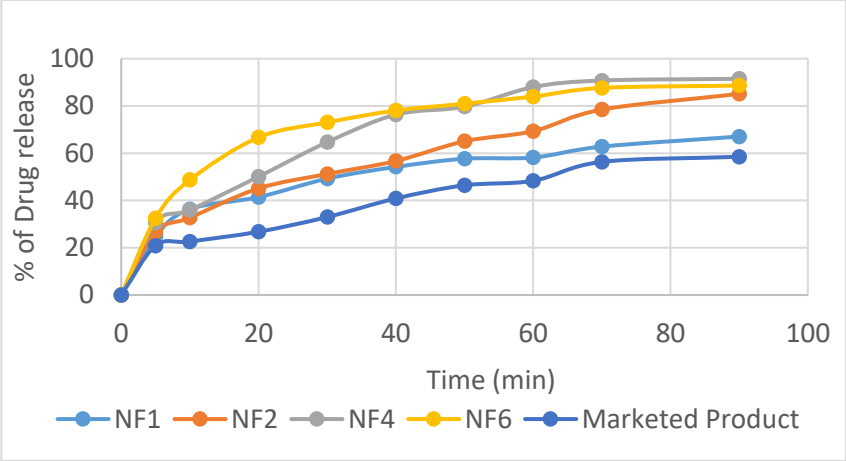

Fig 6 In vitro dissolution

Drug Content :

Calculate the chemical content of the selected sample using the standard formula.) reported values ranging from 97.9% Â± 2.23% to 98..9% Â± 1.12%. The distribution of chemical content corresponds to the group SBF1, SBF2, SBF4 and SBF6.

Table 12 : Percentage of drug in solid SNEDDS

Formulation Code	Percentage of Drug
SBF1	97.9
SBF2	98
SBF4	98.6
SBF6	98.9

In vitro dissolution Test

The percentage of atorvastatin release in SBF4 and SBF6 formulations was found to be higher than other formulations and commercial products (Lipitor 10 mg). The drug release percentage of SBF4 and SBF6 after 90 minutes was 99.49% and 89.26%, respectively, while the release rate of the commercial product was 58.49%. The percentage of drug release is higher in the SBF4 formulation due to lower viscosity and higher surfactant concentration (e.g. Tween 80).

Table 13: In vitro dissolution test for solid SNEDDS

Time (Min)	**Cumulative percentage drug release (%) in phosphate buffer**					
	SBF1 (Mean±SD), n=3	**SBF2** (Mean±SD), n=3	**SBF4** (Mean±SD), n=3	**SBF6** (Mean±SD),	**Marketed formulation** (Mean±SD)	**Drug** (Mean±SD)
0	0	0	0	0	0	0
5	24.25±0.49	26.29±0.87	39.12±1.01	32.46±1.02	16±0.35	8±0.35
10	36.33±0.85	33.71±1.21	58.34±0.95	49.56±1.21	22.64±0.59	10±0.59
20	41.34±0.73	42.72±0.78	71.65±0.75	68.67±1.21	26.64±0.92	12.78±0.92
30	44.62±0.98	51.62±1.41	78.66±1.16	74.65±0.95	34.63±0.88	15.2±0.88
40	49.21±0.98	56.41±1.21	86.89±1.02	79.98±0.95	41.86±0.85	16.95±0.85
50	54.67±1.06	59.35±0.95	91.26±0.88	82.78±0.92	46.42±1.09	18.53±1.09
60	58.66±0.92	63.3±1.13	93.12±0.92	85.55±0.92	48.34±1.15	21.33±1.15
75	62.43±1.43	69.46±1.55	96.66±1.28	87.63±0.88	52.64±1.15	23.52±0.89
90	64.78±1.12	73.10±1.23	99.49±1.43	89.26±0.88	58.49±1.22	25.89±1.22

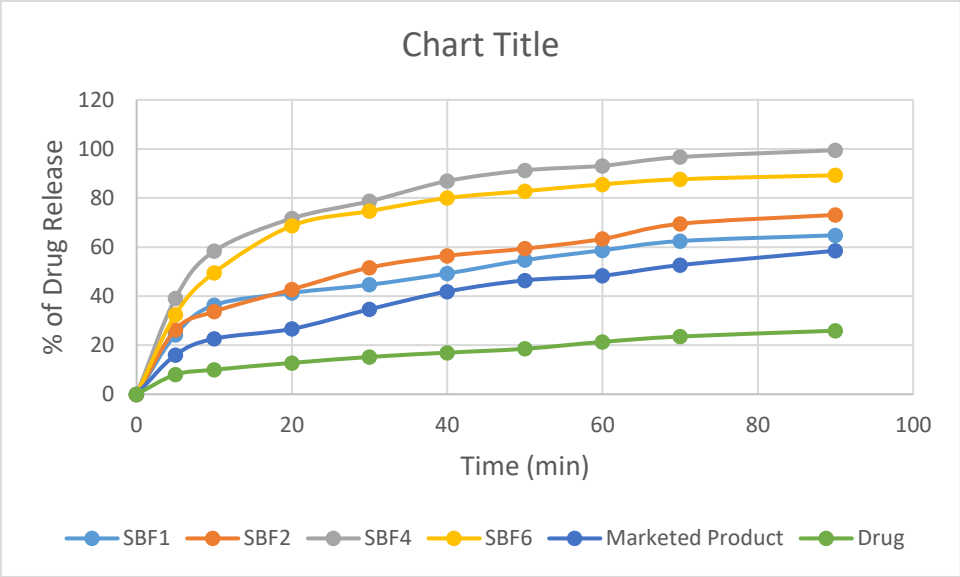

Figure 7: In vitro dissolution test for solid SNEDDS

Stability studies

SBF4 and SBF6 formulations were found to be stable for 2 months without significant change in drug content or particle size. No precipitate is formed in this formulation.

Table 14: Stability for the solid SNEDDS

Formulation code	Sampling point	Droplet size size(nm)	% drug content
SBF4	0 Days	177.5	98.4
	30 Days	177.5	99
	60 Days	179.5	98.2
SBF6	0 Days	161.2	98.78
	30 Days	162	98.67
	60 Days	163.4	98.89

CONCLUSION:

The best atorvastatin loading formulation containing sunflower oil, Tween 80 and PEG 400 has the advantage of improving atorvastatin. Thus, our study confirmed that SNEDDS can be used as an alternative to oral atorvastatin. The results also suggest that SNEDDS can be used as a potential

drug to improve the discrimination of atorvastatin and other adverse drug reactions. Infrared spectroscopy compatibility studies showed no interaction between the drug and the stabilizer. Microemulsion areas were found in Smix (80 to PEG 2:1) compared to other Smix ratios (80 to PEG 3:1). This means that the more surfactant there is in Smix, the larger the microemulsion zone is formed. Sunflower oil nanoemulsions are known to increase the solubility of biopharmaceutical classification class II drugs. Therefore, atorvastatin was chosen as a model drug for inclusion in nanoemulsions due to its poor solubility properties. Atorvastatin-loaded SNEDDS were prepared using an appropriate formulation and their self-nanoemulsifying properties were evaluated. It is included in the system due to its good dissolution efficiency.

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